PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 26788-012	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/US04/19229	International filing date *(day/month/year)* 06 October 2004 (06.10.2004)	Priority date *(day/month/year)* 06 December 2003 (06.12.2003)
International Patent Classification (IPC) or national classification and IPC IPC: **C12N 15/11**(2006.01) USPC:		
Applicant NUCLEONICS INC.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 5 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *(sent to the applicant and to the International Bureau)* a total of ___ sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) _____ , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).
4. This report contains indications relating to the following items:
   - ☒ Box No. I Basis of the report
   - ☐ Box No. II Priority
   - ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - ☒ Box No. IV Lack of unity of invention
   - ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - ☐ Box No. VI Certain documents cited
   - ☐ Box No. VII Certain defects in the international application
   - ☐ Box No. VIII Certain observations on the international application

Date of submission of the demand	Date of completion of this report
11 January 2005 (11.01.2005)	07 January 2007 (07.01.2007)
Name and mailing address of the IPEA/ US Mail Stop PCT, Attn: IPEA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (571) 273-3201	Authorized officer Bo Peng Telephone No. 571-272-1600

Janice Ford for

Form PCT/IPEA/409 (cover sheet)(April 2005)

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US04/19229

Box No. I Basis of the report

1. With regard to the **language**, this report is based on:

☒ the international application in the language in which it was filed.

☐ a translation of the international application into English, which is the language of a translation furnished for the purposes of:

☐ international search (under Rules 12.3 and 23.1(b))

☐ publication of the international application (under Rule 12.4(a))

☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

☒ the international application as originally filed/furnished

☒ the description:
pages 1-88 as originally filed/furnished
pages* NONE received by this Authority on _____
pages* NONE received by this Authority on _____

☒ the claims:
pages 89-95 as originally filed/furnished
pages* NONE as amended (together with any statement) under Article 19
pages* NONE received by this Authority on _____
pages* NONE received by this Authority on _____

☒ the drawings:
pages 1-14 as originally filed/furnished
pages* NONE received by this Authority on _____
pages* NONE received by this Authority on _____

☒ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing.

3. ☒ The amendments have resulted in the cancellation of:

☒ the description, pages None
☒ the claims, Nos. None
☒ the drawings, sheets/figs None
☒ the sequence listing (*specify*): None
☒ any table(s) related to the sequence listing (*specify*): None

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

☐ the description, pages _____
☐ the claims, Nos. _____
☐ the drawings, sheets/figs _____
☐ the sequence listing (*specify*): _____
☐ any table(s) related to the sequence listing (*specify*): _____

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos. 5-8,16,17,22,28 and 29

because:

☐ the said international application, or the said claim Nos. _____ relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. _____ are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☒ no international search report has been established for said claims Nos. 5-8,16,17,22,28 and 29

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b) and 13*ter*.2.

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation to restrict or pay additional fees the applicant has, within the applicable time limit:

   ☒ restricted the claims.

   ☐ paid additional fees.

   ☐ paid additional fees under protest, and, where applicable, the protest fee

   ☐ paid additional fees under protest but the applicable protest fee was not paid

   ☐ neither restricted the claims nor paid additional fees

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is:

   ☐ complied with.

   ☐ not complied with for the following reasons:

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts

   ☒ the parts relating to claims Nos. 1-4, 9-15, 18-21, 30 and 31

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

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Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	3,4,9-12,14,15,18-20,23 and 26	YES
	Claims	1, 2, 13, 21, 24, 25, 27 30 and 31	NO
Inventive Step (IS)	Claims	NONE	YES
	Claims	1-4, 9-15, 18-21, 23-27, 30 and 31	NO
Industrial Applicability (IA)	Claims	1-4, 9-15, 18-21, 23-27, 30 and 31	YES
	Claims	NONE	NO

2. Citations and Explanations (Rule 70.7)
Reference is made to the following documents:
D1: US 6,518,417
D2: Giladi H Molecular Therapy, vol. 8, No. 5, p. 769-776, 2003.
D3: Randall G. PNAS Vol. 100, No. 1, pp 235-240, 2003.

Claims 21, 24, 25, 27, 30 and 31 do not meet the criteria set out in PCT Article 33(2)-(3) as being anticipated by D1.
Claims 21, 24, 25, 27, 30 and 31 are directed to a composition for inhibiting HBV replication comprising at least a 19 contiguous base pair nucleotide sequence, expression vector and cells.
D1 is related to antisense nucleic acids comprising a nucleotide sequence containing at least 19 contiguous base pairs, which are directed against specific sequences of HBV RNA, and vector and host cells. Since D1 meets the limitation of Claims 21, 24, 25, 27, 30, 31, the claims are anticipated by D1. Therefore, the subject matter of Claims 21, 24, 25, 27, 30, 31 lacks novelty. Note: Since CRF has never been received; the claims are reviewed as without specific SEQ ID NOs.

Claims 1, 2, 13 and 21 do not meet the criteria set out in PCT Article 33(2)-(3) as being anticipated by D2.
Claims 1, 2, 13 and 21are directed to a method for inhibiting expression of a polynucleotide sequence of HBV in an *in vivo* mammalian cell comprising administering to the said cell a double-stranded RNA effector molecule comprising an at least 19 contiguous base pair nucleotide sequence of SEQ ID NOs:1-10.
D2 is related to a method of inhibiting HBV infection *in vivo*, comprising administering siRNA to mice. The HBV-specific siRNA is 21-bp. The subject matter of Claims 1, 2, 13 and 21 are anticipated by D2, therefore, lacks novelty. Note: Since CRF has never been received; the claims are reviewed as without specific SEQ ID NOs.

Claims 1-4, 9-15 and 18-20 lack an inventive step under PCT Article 33(3) as being obvious over D2 and D3.
Claims 1-4, 9-15 and 18-20 are directed to a method for inhibiting expression of a polynucleotide sequence of HBV and HCV in an *in vivo* mammalian cell comprising administering to the said cell a double-stranded RNA effector molecule comprising a nucleotide sequence containing at least 19 contiguous base pairs of SEQ ID NOs:1-10. The relevance of D2 is set forth supra. D2 does not teach inhibiting HCV replication using siRNA. D3 teaches siRNA can be used for inhibiting HCV replicon RNAs in cell cultures. It would be obvious for one skilled in the art to use siRNA to inhibit both HBV and HCV. Therefore, in light of D2 and D3, the subject matter of claims 1-4 and 12-17 lacks an inventive step.

Claims 1-4, 9-15, 18-21, 23-27, 30 and 31 meet the criteria set out in PCT Article 33(4), and have industrial applicability because the subject matter claimed can be made or used in industry.

---------- NEW CITATIONS ----------
Randall G. "Clearance of replicating hepetitis C virus replicon RNAs in cell culture by small interfering RNAs" PNAS, Vol. 100, No. 1, pp.235-240, Jan., 7, 2003.

PATENT COOPERATION TREATY

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NOTE ON INFORMAL COMMUNICATION WITH THE APPLICANT

(PCT Rule 66.6)

International application No.	Applicant's or agent's file reference	Date of informal communication *(day/month/year)*
PCT/US04/19229	26788-012	29 September 2006 (29.09.2006)
Applicant NUCLEONICS INC		

Communication

☒ by telephone

☐ personal

Participants

☒ identity checked ☐ authorization checked ☐ personally known

☐ Applicant:

☒ Agent: Jeffery Safran

☒ Examiner(s): Bo Peng

Summary of communication:

Attorney Jeffery Safran gave the examiner a permission to do 409 directly during a phone interview.

☐ An extension of time limit is granted (Form PCT/IPEA/427).

☒ A copy of this note is being sent to the applicant with Form PCT/IPEA/429.

Applicant/Agent	Authorized officer of IPEA/
Jeffery Safran	Bo Peng Telephone No. 571-272-1600

Janice Ford for

Form PCT/IPEA/428 (July 1992; reprint January 2004)